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| EXAMINER | |
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| ART UNIT | PAPER NUMBER |
|---|---|
| 1652 | |

DATE MAILED: 04/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 08/876,276 | SHORT ET AL. | |
| | Examiner | Art Unit | |
| | David J Steadman | 1652 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *09 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *19-41 and 43-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19-41 and 43-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *02/09/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

### *Status of the Application*

**[1]** Claims 19-41 and 43-46 are pending.

**[2]** Applicants' amendment to the claims, filed February 09, 2004, is acknowledged. This listing of the claims replaces all prior versions and listings of the claims.

**[3]** Receipt of an information disclosure statement (IDS), filed February 09, 2004, is acknowledged. All references cited therein have been considered by the examiner and a copy of the IDS is attached to the instant Office action.

**[4]** It is noted that applicants refer to Exhibits A, B, and C in the instant response (see page 9). However, the examiner is unable to locate Exhibits A, B, and C in the instant application.

**[5]** Applicant's arguments filed February 09, 2004 have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

**[6]** The text of those sections of Title 35, U.S. Code not included in the instant action can be found in a prior Office action.

### *Claim Rejections - 35 USC § 112, Second Paragraph*

**[7]** In view of applicants' amendment to claim 24, the rejection under 35 U.S.C. 112, second paragraph, as set forth in item [5] of the Office action mailed October 09, 2003 is withdrawn.

**[8]** Claim 41 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- Claim 41 is indefinite in the recitation of "bioactivity" as the claim depends from claim 40, which limits the "bioactivity" as recited in claim 19 to an "enzymatic activity". It is suggested that applicants maintain consistency of terms used in the claims.
- Claim 41 recites the limitation "the wild-type DNA". There is insufficient antecedent basis for this limitation in the claim. It is suggested that applicants replace the term with, for example, "a corresponding wild-type DNA".
- Claim 41 is confusing in that it is unclear as to whether the "bioactivity encoded by the DNA" as recited in claim 41 is meant to be the DNA obtained from a clone identified in step c) of claim 19 or is the mutant having at least one nucleotide mutation as recited in claim 40. It is suggested that applicants clarify the meaning of the claim.

***Claim Rejections - 35 USC § 112, First Paragraph***

**[9]** The new matter rejection of claim 41 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record (as set forth in item [6] of the Office action mailed October 09, 2003) and for the reasons stated below.

Applicants argue that support for the phrase at issue in claim 41 can be found in original claims 1 and 18. To the extent the rejection is based on the phrase, "the bioactivity encoded by the DNA possesses the bioactivity of interest at a temperature at least 10 °C below the temperature of optimal activity of the bioactivity encoded by the

wild-type DNA", the rejection is withdrawn in view of applicants' cited support for this recitation.

Regarding the recitation of "naturally occurring", applicants argue that support for this phrase is found in original claim 1 by the recitation of "prokaryotic genomic DNA samples". Applicants assert that genomic DNA samples are by definition "naturally occurring". Applicants' arguments are not found persuasive.

It is noted that the DNA as recited in claim 19 is not limited to prokaryotic DNA or to genomic DNA. It is further noted that there is no requirement that "prokaryotic genomic DNA" be "naturally occurring" as such DNA may be obtained, e.g., from a bacterial strain whose genomic DNA sequences have been altered by a mutagen, e.g., UV radiation. As such, one would clearly recognize that the term "prokaryotic genomic DNA" does not provide support for the term "naturally occurring".

Applicants further argue that support for the term "naturally occurring" can be found in the following disclosure: "Preferably 'environmental libraries' which represent the collective genomes of naturally occurring microorganisms are generated" (citing pages 7, 17, and 22 of the specification). Applicants' argument is not found persuasive.

As noted above, there is no requirement in claim 19 that the DNA be limited to being isolated from a microorganism. Clearly applicants' cited support discusses genomic DNA from prokaryotic sources and as such, does not provide support for the term "naturally occurring" in the context of the claim, which recites, "naturally occurring DNA from more than one organism". This recitation encompasses not only prokaryotic genomic DNA, but also eukaryotic genomic DNA. MPEP 2163, in addressing new or

amended claims, states, "newly added claim limitations must be supported in the specification through express, implicit, or inherent disclosure." In view of applicants' failure to demonstrate support in accordance with MPEP 2163, the rejection is maintained.

**[10]** Claims 19-41 and 43-46 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection. Applicants have amended claim 19 to recite the limitation "wherein each clone contains DNA from a single organism". MPEP states, "when filing an amendment an applicant should show support in the original disclosure for new or amended claims (citing MPEP §§ 714.02 and 2163.06). However, the examiner can find no showing for the limitation in the response filed February 09, 2004. Moreover, the examiner can find no support for this limitation in the specification, claims, or drawings as originally filed. In the event the examiner has overlooked such support, applicants are invited to direct the examiner's attention to support for the cited limitation in the specification, claims, and/or drawings as originally filed.

### *Claim Rejections - 35 USC § 102*

**[11]** The rejection of claims 19-20, 22, 24-29, 35, 37-39, and 43-45 under 35 U.S.C. 102(b) as being anticipated by Thompson et al. (US Patent 5,824,485) is maintained for

the reasons of record (as set forth in item [7] of the Office action mailed October 09, 2003) and for the reasons stated below.

Applicants argue that the claimed invention distinguishes over Thompson et al. by requiring that the bioactivity or biomolecule of interest be naturally occurring and be the DNA of a single one of the organisms in the sample. Applicants argue that the claimed invention seeks to "produce libraries of naturally occurring activities or gene clusters or pathways or genes from a single organism as found in nature, without manipulation" using donor DNAs that "have not been rearranged or recombined in a laboratory setting". Applicants' argument is not found persuasive.

The nucleic acids used to construct the library screened by the method of Thompson et al. clearly encompass host cells comprising naturally occurring DNA obtained from a mixed population of organisms, wherein each host cell has DNA from one donor organism. For example, Thompson et al. describe their library as being "a library of expression constructs prepared from genetic material derived from a plurality of species of donor organisms." Thompson et al. teach that "[t]he genetic material in each of the host organism encodes naturally-occurring biochemical pathways... ...from one of the donor organisms" (column 6, lines 17-27). At least from this description of their library, one of ordinary skill in the art would recognize that: 1) the library of Thompson et al. contains clones containing naturally occurring DNA from a single donor organism, i.e., DNA that has not been manipulated, and 2) each host organism contains DNA from one, i.e., a single, donor organism.

Applicants argue that Thompson et al. do not teach the use of "naturally occurring" DNA, but combinatorial DNA, wherein host native DNA combines with donor DNA to produce a "novel compound". Applicants' cite extrinsic evidence (Exhibits A, B, and C) as providing support for the meaning of "combinatorial". Applicants' argument is not found persuasive.

Contrary to applicants' assertion, the examiner has not relied upon the quoted text of Thompson et al. (column 15, top) for defining the term "naturally occurring" as used by Thompson et al. Instead, this text was relied upon by the examiner as evidence that the reference of Thompson et al. teaches that their library encompasses clones comprising DNA from more than one organism (see page 8 of the Office action mailed October 09, 2003).

In this case, applicants have misinterpreted the disclosure of Thompson et al., allegedly suggesting combination of host DNA and donor DNA. While applicants attempt to define "combinatorial" in such a way as to overcome the cited prior art (it is noted that the examiner is unable to locate Exhibits A, B, and C in the instant application and has relied upon the text of page 9 of the instant response for applicants' definition of "combinatorial"), it is clear that the term "combinatorial" as used by Thompson et al. is not meant to be defined as a physical combining of DNAs. Nowhere in this citation is there mention of the combining of DNAs from the host and donor organisms. Instead, this disclosure (column 5, paragraph 1) suggests that the metabolic pathways of the donor can be "reconstituted" in the host, i.e., the donor metabolic pathway present in the host. As the metabolic pathway of the donor organism may not

be present in the host, the interaction or combination of these pathways may generate novel compounds. As such, Thompson et al. is clearly teaching the interaction or combination of metabolic pathways – not the combining of DNAs as asserted by applicants. MPEP 2106 states, "An applicant is entitled to be his or her own lexicographer, and in many instances will provide an explicit definition for certain terms used in the claims" and "[w]here an explicit definition is provided by the applicant for a term, that definition will control interpretation of the term as it is used in the claim". Applicants are referred to the definition of "combinatorial natural pathway expression library" (column 6, lines 17-27). Thompson et al. make clear that the donor DNA contained by the host organism "encodes naturally-occurring biochemical pathways" – not mutant or variant biochemical pathways as asserted by applicants. It should be noted that the "plurality of clones containing naturally occurring DNA from more than one organism, wherein each clone contains DNA from a single organsim" as recited in claim 19 are also likely to express metabolic enzymes from the donor DNA that can combine with the host metabolic pathways – exactly as taught by Thompson et al. In view of applicants' failure to distinguish the claimed invention from the method as taught by Thompson et al., the rejection is maintained.

***Claim Rejections - 35 USC § 103***

**[12]** The rejection of claim 23 under 35 U.S.C. 103(a) as being unpatentable over Thompson et al. is maintained for the reasons of record (as set forth in item [8] of the Office action mailed October 09, 2003) and for the reasons stated below.

Applicants argue Thompson et al. does not teach all limitations of the claim (citing their argument addressing the rejection under 35 USC 102(b)) as claim 23 depends from claim 19. Applicants argue Thompson et al. fail to motivate one to modify Thompson et al. to arrive at the claimed invention because Thompson et al. is allegedly devoted to preparation and screening of combinatorial gene libraries. Applicants argue that the disclosure of "reconstituted metabolic pathways" does not suggest and would not motivate one to look to the DNA of a single donor organism for detection of a "naturally occurring" biomolecule or bioactivity of interest. Applicants' argument is not found persuasive.

The examiner hereby incorporates the response addressing applicants' arguments regarding the rejection under 35 USC 102(b). As stated therein, Thompson et al. teaches the use of naturally occurring DNA from "one of the donor organisms" (column 6, lines 17-27). For these reasons, it is the examiner's position that Thompson et al. teach all limitations of claim 19, from which claim 23 is dependent upon. While Thompson et al. do not teach the use of at least $2 \times 10^6$ clones to practice their method, one would have been motivated to use at least this many clones in order that the statistical probability of identifying a clone comprising an activity of interest would be substantially increased. In view of the teachings of Thompson et al., claim 23 would have been obvious to one of ordinary skill in the art at the time of the invention.

**[13]** The rejection of claims 30-32 and 34 under 35 U.S.C. 103(a) as being unpatentable over Thompson et al. in view of Miao et al. (Biotechnol Bioengineer

42:708-715) is maintained for the reasons of record (as set forth in item [9] of the Office action mailed October 09, 2003) and for the reasons stated below.

Applicants argue Thompson et al. does not teach all limitations of the claim (citing their arguments addressing the rejection under 35 USC 102(b) and 35 USC 103(a) as being unpatentable over Thompson et al.) Applicants argue that, in addition to those previous arguments, Miao et a. fails to remedy the alleged deficiencies of Thompson et al. Applicants argue Miao et al. are silent regarding screening a library containing a plurality of clones obtained from one or more organisms wherein each clone contains DNA from one organism in the multispecies population. Applicants argue that even if one were motivated to combine the cited references, there is no reasonable expectation of success for adapting the technique of Miao et al. to the method of Thompson et al. Applicant's argument is not found persuasive.

The examiner hereby incorporates the response addressing applicants' arguments regarding the rejection under 35 USC 102(b). For these reasons, it is the examiner's position that Thompson et al. teach all limitations of claim 19, from which claims 30-32 and 34 are dependent upon. Based on the motivation for using C12FDG as a fluorgenic substrate to detect those clones expressing beta-galactosidase by FACS, i.e., to prevent substrate leakage (page 708, right column), one would have been motivated to use the substrate of Miao et al. to practice the method of Thompson et al. As Miao et al. demonstrate the use of their substrate in screening a large number of clones, one would have had a reasonable expectation of success for using the substrate of Miao et al. in practicing the method of Thompson et al. In view of

applicants' failure to provide specific and/or convincing reasoning as to why the combination of references fails to teach, provide motivation for practicing, and a reasonable expectation of success for making the claimed invention, the rejection is maintained.

**[14]** The rejection of claim 33 under 35 U.S.C. 103(a) as being unpatentable over Thompson et al. in view of Miao et al. as applied to claims 30-32 and 34 above, and further in view of Hirata et al. (US Patent 4,861,718) is maintained for the reasons of record (as set forth in item [10] of the Office action mailed October 09, 2003) and for the reasons stated below.

Applicants argue Thompson et al. in view of Miao et al. does not render obvious claims 19 and 32 from which claim 33 is dependent upon (citing their arguments addressing the rejection under 35 USC 102(b) and 35 USC 103(a) as being unpatentable over Thompson et al. in view of Miao et al.) Applicants argue Hirata et al. fail to remedy the alleged deficiencies of Thompson et al. and Miao et al. and Hirata et al. are silent regarding screening a library containing a plurality of clones obtained from one or more organisms wherein each clone contains DNA from a single one of the donor organisms. Applicants argue that the cited references fail to motivate one to modify the combined disclosures to arrive at such a method at any temperature. Applicants argue that even if one were motivated to combine the cited references, there is no reasonable expectation of success for practicing the claimed method. Applicants' argument is not found persuasive.

The examiner hereby incorporates the response addressing applicants' arguments regarding the rejection under 35 USC 102(b) and to the rejection of claims 30-32 and 34 under 35 USC 103(a). For these reasons, it is the examiner's position that Thompson et al. in view of Miao et al. teach all limitations of claims 19 and 32, from which claim 33 depends. As previously stated, the combination of references clearly teaches all limitations of the claims and, contrary to applicants' assertion, provides a reasonable expectation of success for practicing the claimed method. In view of applicants' failure to provide specific and/or convincing reasoning as to why the combination of references fails to teach, provide motivation for practicing, and a reasonable expectation of success for making the claimed invention, the rejection is maintained.

**[15]** The rejection of claims 21, 36, 40, and 46 under 35 U.S.C. 103(a) as being unpatentable over Thompson et al. in view of Minshull et al. (US Patent 5,837,458) is maintained for the reasons of record (as set forth in item [11] of the Office action mailed October 09, 2003) and for the reasons stated below.

Applicants incorporate their arguments regarding the rejection of claims 19-20 under 35 USC 103(a) addressing the reference of Thompson et al. Additionally, applicants argue Minshull et al. fails to remedy the alleged deficiencies of Thompson and the combined disclosures of Thompson et al. and Minshull et al. are silent regarding screening a library containing a plurality of clones obtained from one or more organisms wherein each clone contains DNA from a single one of the donor organisms. Applicants argue that the cited references fail to teach the claim limitations. Applicants argue that

even if one were motivated to combine the cited references, there is no reasonable expectation of success for practicing the claimed method. Applicants' argument is not found persuasive.

The examiner hereby incorporates the response addressing applicants' arguments regarding the rejection under 35 USC 102(b), which includes claims 19-20. For these reasons, it is the examiner's position that Thompson et al. teaches all limitations of claims 19-20, from which claims 21, 36, 40, and 46 depend. As previously stated, the combination of references clearly teaches all limitations of the claims and, contrary to applicants' assertion, provides a reasonable expectation of success for practicing the claimed method. In view of applicants' failure to provide specific and/or convincing reasoning as to why the combination of references fails to teach, provide motivation for practicing, and a reasonable expectation of success for making the claimed invention, the rejection is maintained.

**[16]** Claim 41 is rejected under 35 U.S.C. 103(a) as being unpatentable over Thompson et al. in view of Minshull et al. (US Patent 5,837,458) as applied to claims 21, 36, 40, and 46 above, and further in view of Loveland et al. (Appl Environ Microbiol 60 :12-18). Claim 41 is drawn to the method of claim 40, wherein the mutant has a bioactivity at a temperature at least 10 degrees Celsius below the temperature of optimal activity of the wild-type bioactivity.

Thompson et al. disclose the teachings as described previously at item [7] of the Office action mailed October 09, 2003 and Minshull et al. disclose the teachings as described previously at item [11] of the Office action mailed October 09, 2003.

Thompson et al. do not teach their method can be used to identify an enzyme with an optimal temperature at least 10 degrees Celsius below that of a corresponding wild-type.

Loveland et al. teach isolation of a polynucleotide encoding a beta-galactosidase from a psychrotrophic bacterium that exhibited a temperature optimum about 20 degrees Celsius below that of Escherichia coli beta-galactosidase (page 12, abstract). Loveland et al. teach a motivation for identifying beta-galactosidases with high activity at low temperatures by disclosing, "new [beta]-galactosidases, such as ones with high activity levels at low temperatures, might prove useful for removing lactose from refrigerated milk to be consumed by lactose-intolerant individuals" (page 16, right column, bottom) and recognize that "it is possible to screen numerous colonies by using chromogenic substrates" (page 12, left column, bottom).

Therefore, it would have been obvious to one of ordinary skill in the art to practice the method of Thompson et al. to screen for psychrotrophic microorganisms producing beta-galactosidase and to mutate the polynucleotide encoding a cold-active beta-galactosidase obtained from said psychrotrophic microorganisms by the method of Minshull et al. in order to obtain a mutant having a temperature optimum at least 10 degrees below that of wild-type. One would have been so motivated because of the teachings of Loveland et al. as stated above. One would have a reasonable expectation of success for practicing the method of Thompson et al. to screen for psychrotrophic microorganisms producing beta-galactosidase and to mutate the polynucleotide encoding a cold-active beta-galactosidase obtained from said psychrotrophic

microorganisms by the method of Minshull et al. in order to obtain a mutant having a temperature optimum at least 10 degrees below that of wild-type because of the results of Thompson et al., Minshull et al., and Loveland. Therefore, claim 41, drawn to the method described above, would have been obvious to one of ordinary skill in the art.

***Conclusion***

**[17]** Status of the claims:

- Claims 19-41 and 43-46 are pending.
- Claims 19-41 and 43-46 are rejected.
- No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (703) 308-3934. The Examiner can normally be reached Monday-Friday from 7:30 am to 2:00 pm and from 3:30 pm to 5:30 pm. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (703) 308-3804. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

David J. Steadman
Patent Examiner
Art Unit 1652
04-14-04